

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 October 2003 (09.10.2003)

PCT

(10) International Publication Number
WO 03/082322 A1

(51) International Patent Classification⁷: **A61K 38/43**,
38/18, 38/19, 38/00, A61P 29/00, 35/00, 37/00

Road, Stirling, S.A. 5152 (AU). **WATTENBERG, Brian**,
W. [AU/US]; Brown Cancer Centre, 529 S. Jackson Street,
Louisville, KY 40202 (US).

(21) International Application Number: PCT/AU03/00388

(22) International Filing Date: 28 March 2003 (28.03.2003)

(74) Agents: **OBRANOVICH, Tania, D.** et al.; Davies Col-
lison Cave, 1 Little Collins Street, Melbourne, VIC 3000
(AU).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

PS 1448	28 March 2002 (28.03.2002)	AU
PS 1538	5 April 2002 (05.04.2002)	AU
PS 1621	8 April 2002 (08.04.2002)	AU
2002951668	19 September 2002 (19.09.2002)	AU
2003900230	21 January 2003 (21.01.2003)	AU

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,
SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.

(71) Applicant (*for all designated States except US*): **MED-
VET SCIENCE PTY. LTD.** [AU/AU]; 20 Dalgleish
Street, Thebarton, S.A. 5031 (AU).

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **PITSON, Stuart**,
M. [AU/AU]; 1B Threlfall Avenue, Norwood, S.A. 5067
(AU). **XIA, Pu** [AU/AU]; 97 Shakespeare Avenue, Magill,
S.A. 5072 (AU). **MORETTI, Paul, A.** [AU/AU]; 3 Rail-
way Terrace South, Goodwood, S.A. 5034 (AU). **VER-
WEY, Julia, R.** [AU/AU]; 27 Highfield Drive, Hillbank,
S.A. 5112 (AU). **VADAS, Mathew, A.** [AU/AU]; 8 Branch

Published:

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: A METHOD OF MODULATING CELLULAR ACTIVITY

(57) Abstract: The present invention relates generally to a method of modulating cellular activity and to agents for use therein. More particularly, the present invention provides a method of modulating cellular activity by modulating phosphorylation of sphingosine kinase and, thereby, its activation. In a related aspect, the present invention provides a method of modulating sphingosine kinase functional activity via modulation of its phosphorylation and agents for use therein. The present invention still further extends to sphingosine kinase variants and to functional derivatives, homologues or analogues, chemical equivalents and mimetics thereof exhibiting reduced and/or ablated capacity to undergo phosphorylation. The method and molecules of the present invention are useful, *inter alia*, in the treatment and/or prophylaxis of conditions characterised by aberrant, unwanted or otherwise inappropriate cellular and/or sphingosine kinase functional activity. The present invention is further directed to methods for identifying and/or designing agents capable of modulating sphingosine kinase phosphorylation.

WO 03/082322 A1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU03/00388

A. CLASSIFICATION OF SUBJECT MATTER												
Int. Cl. ⁷ : A61K 38/43, A61K 38/18, A61K 38/19, A61K 38/00, A61P 29/00, A61P 35/00, A61P 37/00												
According to International Patent Classification (IPC) or to both national classification and IPC												
B. FIELDS SEARCHED												
Minimum documentation searched (classification system followed by classification symbols) Refer to electronic database consulted below												
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched												
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) DWPI and MEDLINE. Keywords: sphingosine kinase or sphk or sph kinase, proline directed kinase, ERK, CDK2, TNF, U0126 or PD98059												
C. DOCUMENTS CONSIDERED TO BE RELEVANT												
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.										
X	WO 99/12533 A (MEDVET SCIENCE PTY.LTD) 18 March 1999 Whole document	1-45										
X	WO 01/85953 A (MEDVET SCIENCE PTY.LTD) 15 NOVEMBER 2001 Whole document	1-45										
X	BLAUKAT, A et al. Activation of sphingosine kinase by the bradykinin B ₂ receptor and its implication in regulation of the ERK/MAP kinase pathway. Biol. Chem. January 2001, vol. 382, pages 135-139	1-9, 12-20, 28-36, 44 and 45										
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex												
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention											
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone											
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art											
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family											
"P" document published prior to the international filing date but later than the priority date claimed												
Date of the actual completion of the international search		Date of mailing of the international search report 29 MAY 2003										
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No. (02) 6285 3929		Authorized officer ANDREW ACHILLEOS Telephone No : (02) 6283 2280										

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU03/00388

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MACHWATE, M et al. Sphingosine kinase mediates cyclic AMP suppression of apoptosis in rat periosteal cells. Molecular Pharm. 1998, vol. 54, pages 70-77 Abstract, Col. 2, page 76 onwards	1-45
X	CUVILLIER, O et al. Sphingosine-1-phosphate antagonizes apoptosis of human leukemia cells by inhibiting release of cytochrome c and Smac/DIABLO from mitochondria. Blood, November 2001, Vol. 98(9), pages 2828-2836 Abstract, Col. 2, lines 24 onwards	1-45
X,P	Johnson, KR, et al. PKC-dependent activation of sphingosine kinase 1 and translocation to the plasma membrane. J. Biol. Chem. September 2002, vol. 277 (38), pages 35257-35262	1-45
X,P	MACEYKA, M et al. Sphingosine kinase, sphingosine-1-phosphate, and apoptosis. Biochimica et Biophysica Acta, 2002, Vol. 1585, pages 193-201 Whole document	1-47
X,P	WO 02/098458 A (MEDVET SCIENCE PTY.LTD) 12 December 2002 Page 15, paragraph 2 Pages 19 and 20, and claims 1, 2, 9, 10, 19, 20	1-45

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU03/00388

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	99/12533	EP	1011654	JP	2001515857T	CA	23002838
WO	02/098458						
WO	01/85953	AU	56001/01				END OF ANNEX